REMARKS

Amendments

"Leukemia" is deleted from claim 19.

"Modification" in claim 19 is replaced by "substitution," as supported on page 15, lines 23-26, for example.

Claim 19 further specifies that the "Fc region of the variant is not a native sequence Fc region" as supported on at least page 13, lines 19-22.

Claims 20-21 are amended to refer to the EU numbering system as supported on page 12, lines 16-20, for example.

New claims 22 to 24 are added, with support therefor being found at least as follows:
claim 22 - original claims 1, 4, and 12
claim 23 - original claims 1 and 11
claim 24 - original claim 1, and page 28, line 24

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

Section 112, second paragraph

Claims 20-21 are rejected as indefinite for not reciting the numbering system. Applicants have followed the Examiner's suggestion and amended the claims to refer to the EU numbering system. Reconsideration and withdrawal of the rejection is respectfully requested.

Section 112, first paragraph

Claims 19-21 are rejected under 35 USC Section 112, first paragraph. The Examiner contends that the specification fails to enable:

(1) "at least one amino acid modification in the Fc region,"

(2) "one or more amino acid substitutions," and

(3) "treating any leukemia."

The rejection concerning (1) and (3) is obviated by the amendment of claim 19 to delete "leukemia" and replace "modification" with "substitution." With this amendment, Applicants understand the rejection of claims 20 and 21 falls. The Examiner appears to accept that the specification does disclose that at least certain substitutions of the amino acid residues in the Fc region of IgG antibody can improve binding affinities to the Fc receptors and improve ADCC (Office Action, page 4, second paragraph). Thus, Applicants submit that the rejection of claims 20 and 21 should be withdrawn.

Applicants turn now to the rejection concerning (2), namely "one or more amino acid substitutions" as in claim 19. Said claim, as amended herein, reads:

> A method for treating lymphoma in a mammal comprising administering to the mammal a therapeutically effective amount of a variant of a parent antibody which binds CD20 and comprises an Fc region, which variant mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of human effector cells more effectively than the parent antibody and comprises at least one amino acid substitution in the Fc region, wherein the Fc region of the variant is not a native sequence Fc region.

The present application discloses, for the first time, how to make and identify CD20 antibody variants with improved ADCC function. This is a pioneering invention worthy of claim scope commensurate with the important contribution to the field. While the preferred embodiment is a 298/333/334 variant, many Fc region residues are identified which can be modified to generate ADCC-improved variants. See Example 4 on pages 70- 89. The residues which can be altered to improve ADCC include: 256, 290, 298, 312, 326, 330, 333, 334, 360, 378, and 430 (see

specification, page 28, lines 29-30, for example). Thus, the specification contains *numerous working examples* of variants comprising at least one amino acid substitution. Moreover, the specification provides *ample guidance* on *how to make* additional variants comprising at least one substitution and further describes *how to screen* for improved ADCC function either directly (specification, page 34, lines 9-14 and Example 4, by way of example) or indirectly via evaluating FcγR binding (specification, page 34, lines 3-8, page 35, line 25 through page 37, line 12, Examples 1 and 4, for instance). Thus, the skilled person, following the teachings of the present application, can practice the claimed invention across its scope insofar as many different CD20 antibody Fc variants can be made and identified with the claimed improved ADCC function. Finally, Applicants note that there is precedent for the Patent Office to recognize the important contribution of the present invention by granting claims that do not necessarily recite specific amino acid residues and positions in the Fc region (*e.g.* claim 1 of US Patent No. 6,737,056). For any and all of these reasons, Applicants submit that the CD20 antibody variant in claim 19 is enabled.

Applicants have further provided evidence demonstrating the *in vivo* efficacy of the claimed variants. In particular, US patent publication, US2006/0246004 A1, describes various CD20 antibody Fc variants with improved ADCC function (Examples 3, 6, and 12-13), including 2H7.v31, 2H7.v511, and 2H7.v114. Such variants were shown to be effective at B-cell depletion in mammals, see Examples 9, 15-16, and 18-19. Thus, Applicants further submit that the method of claim 19 using the CD20 antibody variants is enabled.

The Examiner relies on Lund *et al. J. Immunol.* 157: 4963-4969 (1996) as allegedly showing that "even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody and therefore influence its effector functions of Fc receptor binding and complement activation." Applicants submit that such is insufficient evidence to support a lack of enablement rejection with respect to the present claims.

Applicants submit that Lund is irrelevant to the variant in claim 19 herein which "mediates

antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of human effector cells more effectively than the parent antibody." Lund was evaluating C1q binding, complement-dependent lysis, or superoxide production through human FcγRI (Figs. 1-4), not ADCC function as in claim 19 herein. Thus, Applicants submit Lund is irrelevant to the presently claimed invention. In any event, the present application provides experimental evidence supporting *many* variants with improved ADCC function (including those with substitutions at one or more of positions 256, 290, 298, 312, 326, 330, 333, 334, 360, 378, and 430). Such would be more probative as to the enablement of claim 19 than the studies in Lund evaluating different variants for different functions. Additionally, the present application further describes how to make and screen for yet additional variants with improved ADCC function. While the specification explains that not all variants will have improved ADCC function, it describes how to screen a panel of variants to identify those with the claimed function. Such screening would not be considered undue experimentation in view of the disclosure of the present application and the level of skill in the art at the filing date. Thus, Applicants submit that Lund simply fails to demonstrate that claim 19 herein is not enabled.

Reconsideration and withdrawal of the Section 112, first paragraph enablement rejection is respectfully requested.

Section 102(e)

Claim 19 is rejected under 35 USC Section 102(e) as being anticipated by US Patent No. 5,736,137 to Anderson. This rejection is obviated by the amendment herein to specify that "the Fc region of the variant is not a native sequence Fc region." Reconsideration and withdrawal of the Section 102(e) rejection is respectfully requested.

Section 102(e)

Claims 19-21 are rejected under 35 USC Section 102(e) as being anticipated by US Patent No. 6,528,624 Idusogie *et al.* ("the '624 patent").

First, Applicants submit that the rejection of claim 20 is misplaced insofar as that claim recites "substitutions at positions 298, 333 and 334." The Examiner has nowhere explained where that "triple-variant" is disclosed by the '624 patent. Withdrawal of the rejection of claim 20 is respectfully requested.

Second, Applicants traverse the 102(e) rejection of claims 19 and 21. Applicants note that this is an anticipation rejection (not an obviousness rejection[1]). In order for a prior art reference to *anticipate*, every element of the claimed invention must be identically shown in a single reference. Claims 19 and 21 herein concern "treating lymphoma." Column 34, lines 66-67 of the '624 patent refers to treating "cancer." Applicants submit that, insofar as "cancer" would not disclose the species "lymphoma," the 102(e) rejection should be withdrawn.

In addition, Applicants point out that the "polypeptide variants"of the invention in the provisional application 60/080,447 filed April 2, 1998 (to which the '624 patent claims priority) comprised an amino acid substitution at position 329, or at two or all of amino acid positions 329, 331, and 322 (see "Summary of the Invention"). Such were the polypeptide variants described for *in vivo* uses at column 34, lines 60-67. Given that column 40, lines 51-55 of the '624 patent explained that K334 had "little or no effect on C1q binding" Applicants submit that such K334 variant would not have been picked for the therapeutic methods described at columns 34-35, at least not according to the disclosure of the 60/080,447 application[2].

Thus, Applicants submit that the Section 102(e) rejection based on the '624 patent should be withdrawn.

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[1] The '624 patent is not available for "obviousness" purposes, since 35 USC Section 103(c)(1) excludes such subject matter, which was owned by the same person or subject to an obligation of assignment to the same person (Genentech) at the time the claimed invention was made.

[2]Applicants have earlier explained that the subject matter in the '624 patent that was not included in provisional application 60/080,447 filed April 2, 1998 is not available even for novelty purposes under 35 USC Section 102(e).

Statement of Related Cases

The following application is related to the above-identified application:

U.S. Serial No. 11/871,335 filed 10/12/2007.

Other US patents or applications related to the above-identified application have been cited by US patent or publication number in IDS(s) of record, or in the IDS filed herewith. Applicants request that the Office consider each of these related patents or applications with respect to the above application.

Applicants believe this application is now in condition for allowance, and look forward to early notification to that effect.

Respectfully submitted,
GENENTECH, INC.

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